REMARKS/ARGUMENTS

Claim status. Claims 29, 46 to 51, and 63 to 68 are currently pending. Claims 29 and 46 are amended hereby. Claims 40, 69, 70, and 71 are canceled hereby. No claim has been added.

Support for amendments. The amendment to the abstract merely presents subject matter present in the specification and in original claims 26, 27, and 28. No new matter is added to the abstract.

The amendment to Claim 46 regarding steps (b) and (c) brings the subject matter of previously dependent Claim 28 into the claims and so does not add new matter.

Claim 29 depended from Claim 28, which in turn depended from Claim 46, so the amendment merely corrects the dependency and does not add new matter.

Rejection under Section 112, second paragraph. The Office Action described the use of "incorporating at least one..." as unclear. (Office Action at page 3). The Office Action also alleged that Claim 46 recites a selected peptide rather than a gene. *Id.*

The claim as previously presented recites "selecting ... at least one peptide sequence"; the intention of the claim as previously presented was that the *sequence* of the peptide is selected and then incorporated into the compound in step (b). The Applicants continue to contend that the prior claims were clear and complete. Nevertheless, in the interest of furthering prosecution, the Applicants hereby amend Claim 46. As amended, Claim 46 merely states in one claim the subject matter of Claim 28 and former Claim 46. As shown in Claim 46, one selects the sequence encoding a peptide, prepares a gene construct comprising the selected sequence, and expresses the polypeptide. Claim 46 as amended is supported by the prior claim set (Claims 28 and 46) and by the specification (""Method of Making," pp. 75-76, and "Working Examples," pp. 89-127). The Applicants thus respectfully request that the Examiner withdraw the rejection under Section 112, second paragraph.

The Office Action also said that Claim 40 is confusing and unclear and that Claims 69 to 71 fail to further limit the invention. The Applicants hereby cancel those claims in the interest of compact prosecution and so render the rejections moot.

Double Patenting. The Office Action provisionally rejected Claims 28, 29, 40, 46-51 and 63-71 under the judicially created doctrine of obviousness-type double patenting over claims of co-pending related applications. The Applicants urge withdrawal of this ground of rejection for the reasons below.

As an aid to the Examiner, the Applicants provide a table below listing the related applications and their claimed subject matter. Some of the following family members were *not* cited in the Office Action.

U.S. Serial No. (U.S. Pat. No.)	Attorney Docket No.	Status	Claim type	Activity of peptide recited in claims
09/428,082 (6,660,843)	A-527	Patent	Composition of matter	IL-1 antagonist
09/563,286	A-527A	Pending	Process	Modulates activity of a protein of interest
10/609,217	A-527B	Allowed	Composition of matter	EPO-mimetic
10/632,388 (7,189,827)	A-527C	Patent	Composition of matter	TPO-mimetic
10/645,761	A-527D	Abandoned	Composition of matter	NGF binding
10/645,784 (present app.)	A-527E	Pending	Process	Modulates activity of AGP-3
10/651,723 (7,169,905)	A-527F	Patent	Composition of matter	GCSF-mimetic
10/653,048 (7,186,810)	A-527G	Patent	Composition of matter	Binding to TNF-alpha
10/666,696	A-527H	Abandoned	Composition of matter	Ang-2 binding
11/472,070	A-527I	Pending	Process	Ang-2 binding
11/591,002	A-527J	Pending	Process	NGF-binding

The double patenting rejection conflicts with the restriction requirement (dated 12/12/00) from the '082 application. The restriction requirement found claims to processes to be patentably distinct from claims to compositions of matter. The restriction requirement in the '082 application also stated, "It is noted that there are over 1000 peptide sequences in the instant application and absent any evidence to the contrary, each is presumed to be a distinct species." (office action dated 12/12/00 at page 3). The election of species and resulting amendments in that application led to the patent family noted above.

The present application is now limited to process claims employing the sequences of peptides that modulate the activity of AGP-3. In the interest of compact prosecution, the Applicants provide the terminal disclaimer enclosed herewith, which is directed toward the applications also claiming processes, namely those listed below.

U.S. Serial No. (U.S. Pat. No.)	Attorney Docket No.	Status	Claim type	Activity of peptide recited in claims
09/563,286	A-527A	Pending	Process	Modulates activity of a protein of interest
10/645,784 (present app.)	A-527E	Pending	Process	Modulates activity of AGP-3
11/472,070	A-527I	Pending	Process	Ang-2 binding
11/591,002	A-527J	Pending	Process	NGF-binding

In view of the enclosed terminal disclaimer, the Applicants respectfully request that the double patenting rejection over the '286, '070, and '002 applications be withdrawn.

The Applicants contend that the aforementioned restriction requirement precludes double patenting over the '082, '217, '388, '723, and '048 applications. The restriction requirement found process and composition of matter to be patentably distinct, and the cited applications further concern compositions of matter with distinct activity. For these reasons, the Applicants respectfully request that any double patenting rejection over these applications be withdrawn.

Rejection under Section 103. The arguments raised in the Office Action under Section 103 are (1) the applicants' arguments that the library is formed from random mutagenesis are not commensurate in scope with the claims; and (2) there is nothing in the claims to preclude the natural protein of Chamow (Office Action at page 7).

In response to the contention designated as (1) above, the Applicants call the Examiner's attention to the following excerpt from the specification:

> Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. ... ***In such libraries, random peptide sequences are displayed*** by fusion with coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an antibody-immobilized extracellular domain of a receptor. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify key residues within one or more structurally related families of peptides. (page 3, lines 1-16; emphasis added).

The foregoing excerpt refutes the Examiner's contention that the Applicants' prior arguments are not commensurate in scope with the claims. As noted in the excerpt, a phage display library is composed of random peptide sequences.

The contention designated (2) above is inconsistent with the U.S. Supreme Court's decision in *KSR v. Teleflex,* 17 S. Ct. 1727, 82 USPQ 2d 1385 (2007).

In the Section 103 rejection, the Examiner noted, "What is important is that the claimed method of preparing a pharmacologic agent by fusing it to a Fc is known in the art, irrespective of the peptide preparation...." (Office Action at pages 10-11). The Examiner thus seems to regard the separate existence of phage display and Fc fusion as sufficient to render the claimed invention obvious. In *KSR*, although the Supreme Court criticized the Federal Circuit's rigid teaching/suggestion/motivation test, the Court recognized that:

> "...a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.... [I}nventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. "

Id. at page 15. In short, mere citation of references teaching elements of the claimed invention is not enough, and here the Office Action has supplied no more than that.

The *KSR* decision also reaffirmed the principles the Supreme Court described in *Graham v. John Deere,* 383 U.S. 1 (1966). In that case, the Supreme Court said that secondary considerations, such as long felt need and commercial success, were relevant in determining obviousness. Here, the Applicants claim a process leading to a pharmacologically active molecule that modulates the activity of AGP-3. Using the claimed process, such molecules were actually identified. See Tai *et al.,* "The BAFF inhibitor AMG523 blocks adhesion and survival of human multiple myeloma cells in the bone marrow microenvironment: clinical implication " (copy enclosed; note that "BAFF" is another name for AGP-3). Molecules from the related applications have also proven useful, including in clinical trials. See, e.g., Bussel *et al.*, "AMG 531, a Thrombopoiesis-Stimulating Protein, for Chronic ITP," *New England J. Med.* 355:1672-1681 (2006) (copy enclosed; see, in particular, Figure 1). Despite the therapeutic need for and resulting commercial potential of such therapeutic agents, such molecules were only developed by the assignee of the application subsequent to the filing of the parent application.

The Supreme Court also chastised the Federal Circuit for applying "rigid preventative rules that deny factfinders recourse to common sense." (*Id.* at page 17). Here, the 103 rejection is based on unsupported speculation that one will select from a random library a natural sequence that has the activity of interest. Even if that allegation were true, it is irrelevant—the claim is to the process, not the molecules it produces. Claims for screening assays of small molecule libraries have been recognized as patentable, even though a large number of the molecules screened are known. More to the point, the Office Action does not discuss the vast number of sequence permutations contained in a phage display library, nor the resulting chances of selecting a known sequence from such a library. A finding of obviousness

based on such a remote, speculative basis seems at odds with the Supreme Court's call for common sense in review of obviousness.

Conclusion. In light of the foregoing amendments and remarks, the Applicants respectfully request entry of all amendments and allowance of all claims.

The Commissioner is hereby authorized to charge any filing fees that may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

Respectfully submitted,

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